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Clarithromycin (Biaxin®) extended-release tablet: a therapeutic review

Mark H Gotfried

Clarithromycin (Biaxin®) extended-release tablets, an advanced generation macrolide, were recently introduced into the USA for the treatment of acute exacerbations of chronic bronchitis, community-acquired pneumonia and acute maxillary sinusitis. The reformulation is intended to improve both patient compliance and tolerability. The extended-release tablets allow convenient once-daily dosing (1000 mg). The extended-release formulation has been shown to be equivalent to the immediate-release formulation concerning area under the plasma concentration time curve. In comparative clinical trials for acute exacerbations of chronic bronchitis, community-acquired pneumonia and acute maxillary sinusitis, clarithromycin extended-release tablets were equivalent to the immediate-release formulation concerning clinical efficacy and bacterial eradication, with improved gastrointestinal tolerability. Similar efficacy and gastrointestinal tolerability results were demonstrated in a recent comparative study of clarithromycin extended-release formulation and amoxicillin-clavulanate in patients with acute exacerbations of chronic bronchitis. Clarithromycin extended-release 1000 mg daily has also been shown to be equivalent to levofloxacin 500 mg daily for the treatment of community-acquired pneumonia in a recent study. The macrolide class of antimicrobials, including clarithromycin extended-release, continues to be a safe and efficacious choice for the out-patient management of community-acquired bacterial respiratory tract infections.

Expert Rev. Anti-infect. Ther. 1(1), 9–20 (2003)

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KEYWORDS:
acute exacerbations of chronic bronchitis, clarithromycin extended-release, community-acquired pneumonia, sinusitis,

With the introduction of erythromycin in the 1950s, an alternative to β-lactam therapy became available for the treatment of respiratory tract, skin and soft tissue infections. Erythromycin exhibited a broader spectrum of activity than the β-lactams in that it was also active against atypical pathogens common in lower respiratory tract infections, including chlamydia, mycoplasma and legionella species. However, due to its poor tolerability profile, mainly gastrointestinal adverse effects, patient compliance became an issue leading to concerns over hazards involved with inadequate dosing. In an effort to address these issues, development of clarithromycin (Biaxin®, Abbott Laboratories, IL, USA) began in the 1980s and was introduced into the US market in 1991. Clarithromycin proved to be successful not only in enhancing the spectrum of activity, particularly against *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* but also improving the adverse event profile experienced with erythromycin.

Currently, clarithromycin is a well-established, semisynthetic, second-generation macrolide antibiotic available in various formulations worldwide, including tablets, granules for oral suspension, sachet and intravenous injection. In an effort to improve tolerability, which is postulated to contribute to poor compliance and the emergence of resistant strains of pathogens, clarithromycin was reformulated as an extended-release tablet for once-daily administration and approved for the treatment of acute exacerbations of chronic bronchitis (AECB), community-acquired pneumonia (CAP) and acute maxillary sinusitis (AMS) in the USA in 2001 [1,2].

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Clarithromycin extended-release tablets are equivalent to clarithromycin immediate-release tablets with respect to the area under the plasma concentration–time curve (AUC) despite maximum plasma clarithromycin concentrations being lower and reached later with the clarithromycin extended-release tablets. Equivalence based upon AUC is also achieved between the formulations for the microbiologically active metabolite, 14-hydroxy-clarithromycin.

Compound introduction

Clarithromycin immediate-release tablets were first introduced for the treatment of CAP, AECB, AMS and pharyngitis/tonsillitis as well as for skin and soft tissue infections caused by susceptible organisms. It has subsequently been approved in several countries for other indications, such as the treatment and prophylaxis of disseminated *Mycobacterium avium* complex (MAC) infection in AIDS patients and as combination therapy for the eradication of *Helicobacter pylori* in the treatment of peptic ulcer disease.

In total, clarithromycin extended-release has been studied in over 2000 patients and is considered safe and efficacious for the following indications [3]:

- CAP due to *H. influenzae, Mycoplasma pneumoniae, Streptococcus pneumoniae or Chlamydia pneumoniae* (TWAR)
- AMS due to *H. influenzae, M. catarrhalis* or *S. pneumoniae*
- Acute bacterial exacerbations of chronic bronchitis due to *H. influenzae, Haemophilus parainfluenzae, M. catarrhalis* or *S. pneumoniae*

While it is not approved for use in the treatment of pharyngitis/tonsillitis in the USA, clarithromycin extended-release has shown efficacy in the treatment of pharyngitis/tonsillitis due to *S. pyogenes* as an alternative to first-line therapy (e.g., penicillin) in patients unable to use first-line therapy.

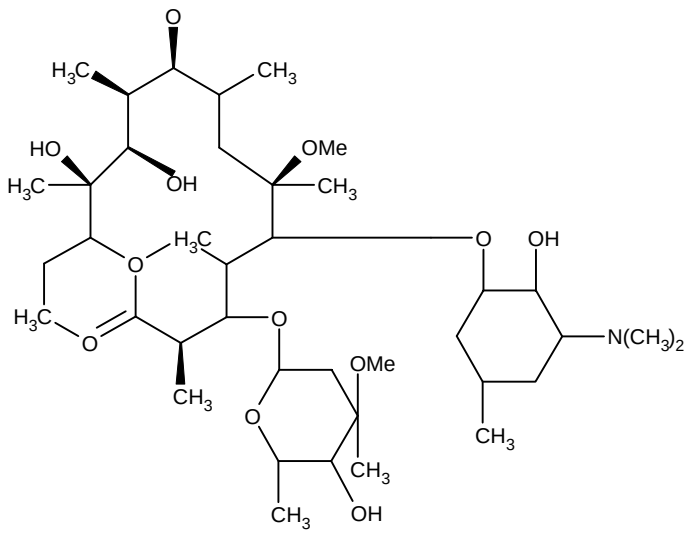

Figure 1. Clarithromycin.

Chemistry

Clarithromycin is a semisynthetic macrolide antibiotic. Chemically it is 6-O-methylerythromycin. The molecular formula is C38H69NO13. The formulae structure is provided in FIGURE 1.

Clarithromycin and erythromycin both have a 14-member macrocyclic lactone system containing glycosidic bonds [4]. Clarithromycin is synthesized by substituting the C6 hydroxy group of erythromycin with a methoxy group. The modification of erythromycin to create clarithromycin, via methylation of the C6 hydroxy group, yields a macrolide with improved potency against several organisms, including *H. influenzae*, *M. catarrhalis* and *S. aureus* [5]. Acid stability is improved by the methylation of the hydroxy group, which has been suggested to improve gastrointestinal absorption and decrease gastrointestinal adverse events [6].

Clarithromycin extended-release 500 mg tablets are formulated using a patented polymer-based matrix that slows the release of clarithromycin and extends absorption from the gastrointestinal tract after oral administration. Relative to an equal total daily dose of IR clarithromycin tablets, clarithromycin extended-release tablets provide lower and later steady-state peak plasma concentrations but equivalent 24-h AUCs and similar steady-state trough plasma levels for both clarithromycin and its microbiologically active metabolite, 14-hydroxy-clarithromycin [7].

Pharmacodynamics

A discussion concerning antimicrobial pharmacodynamics in the context of this review will refer to the correlation of drug concentration and clinical effect. A pharmacodynamic discussion needs to be based not only upon the pharmacokinetic disposition of clarithromycin extended-release but also on the *in vitro* activity of clarithromycin against the primary pathogens associated with respiratory diseases (CAP, AMS and AECB) covered within this review. However, pharmacodynamic modeling, currently a vast source of literature for antimicrobials, should be kept in proper context concerning patient care. Well-controlled clinical data gained from the complex human model outweighs the most logically appealing pharmacodynamic models. The infectious disease end-points are bacterial killing and hopefully improved clinical outcomes.

Clarithromycin exerts its antibacterial effect by binding to the 50S ribosomal subunit of susceptible microorganisms, resulting in inhibition of protein synthesis. Specifically, clarithromycin reversibly binds to the 23S RNA of the 50S subunit. Inhibition of peptidyl transferase blocks the translocation of peptidyl transfer RNA from the amino acid site to the polypeptide site [8]. It is important to note that clarithromycin, like other macrolides, can exert bactericidal effects upon certain species of bacteria, depending on increased drug concentration at the site of infection, smaller inoculum size, alkalinity versus acidity, and a rapid bacterial growth phase [9].

Clarithromycin is active against a variety of aerobic and anaerobic Gram-positive and -negative microorganisms [10]. Additionally, the 14-OH clarithromycin metabolite also has clinically significant antimicrobial activity. Perhaps most notably, the 14-OH metabolite is twice as active as the parent compound against *H. influenzae*.

Clarithromycin is highly active against Gram-positive bacteria, including *S. pneumoniae* and *S. pyogenes*. Clarithromycin is considered to be two- to fourfold more active than erythromycin against most streptococci [9]. Clarithromycin also exhibits good *in vitro* activity against other common respiratory pathogens, including *H. influenzae*, *M. catarrhalis*, *H. parainfluenzae*, *C. pneumoniae*, *M. pneumoniae* and *Legionella pneumophila* [9,11]. Refer to TABLE 1 for the comparative *in vitro* activity of erythromycin, azithromycin and clarithromycin [9,12].

Recently, reports of bacterial resistance concerning the macrolide class of antimicrobials have received increased attention. The primary mechanisms of resistance concerning macrolides and respiratory pathogens include [9]:

- Efflux pumps encoded by a *mef*E gene for *S. pneumoniae* and a *mef*A gene for *S. pyogenes*
- Alteration of the 23S ribosomal RNA of the 50S ribosomal subunit by methylation of adenine, which is encoded by the *erm* gene

The *erm* method of resistance may be constitutive or inducible and is responsible for a pattern of resistance identified as MLSb, conferring resistance to macrolides (M), lincosamides (L) and streptogrammin type b (Sb). In the USA, the efflux pump mechanism of resistance (MIC values of 2–16 µg/ml) is the primary mechanism associated with *S. pneumoniae* resistance (~65%) compared with the ribosomal methylation (MIC values of 32 to >256 µg/ml) mechanism (~35%) [13]. Resistant strains of *S. pneumoniae* were first reported in the USA over 30 years ago. Beginning in the early 1990s, the overall rate of resistance for *S. pneumoniae* began to increase rapidly, with approximately 22% of strains being reported as being intermediately penicillin susceptible (15%) or penicillin resistant (7%) [14]. Only 71% of isolates were considered susceptible to erythromycin. A retrospective analysis was recently completed to determine if increasing resistance rates of *S. pneumoniae* modified the clinical efficacy of clarithromycin in patients being treated AECB and CAP [13]. Based upon the results of the analysis for three separate AECB trials and one CAP trial, increasing rates of reported *in vitro* resistance for *S. pneumoniae* has not had a significant effect on the eradication and clinical response to clarithromycin therapy [13]. Continued analysis of increasing resistance rates for community-acquired respiratory tract pathogens, including *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* and potential impacts on patient outcomes will need to continue for not only the macrolides but also the β-lactams and newer fluoroquinolones.

How does one interpret the potential clinical effects of clarithromycin extended-release from a pharmacodynamic perspective? As noted in the pharmacokinetic section of this review, the extended-release formulation is equivalent to the immediate-release formulation based upon the area under the plasma-concentration curve. Several pharmacokinetic/pharmacodynamic parameters have been proposed as being important determinants of the *in vivo* activity of clarithromycin: duration over the dosage interval that concentrations exceeded the MIC (T > MIC) or the AUC:MIC ratio [15]. The distribution of clarithromycin, not only into serum but also into intracellular (alveolar macrophages), and epithelial compartments (epithelial lining fluid), has been well-described [16]. The clarithromycin extended-release formulation, similar to the immediate-release formulation, concentrates significantly

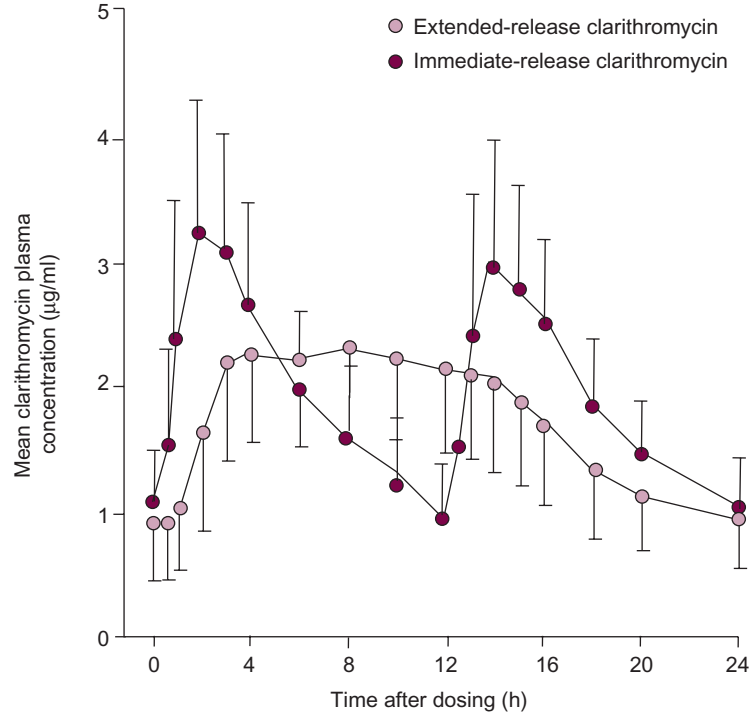

Figure 2. Steady-state clarithromycin plasma concentration time profiles [30]. Study 1: mean (± SEM) steady-state (day 5) plasma concentration–time profiles for clarithromycin extended-release (ER) (two 500-mg tablets once-daily for 5 days with food) and clarithromycin immediate-release (IR) (one 500-mg tablet twice-daily for 5 days with food).
Adapted from Guay *et al. Clin. Therapeut.* (2001).

higher in epithelial lining fluid (4- to 25-times) and alveolar macrophages (300- to 500-times), in comparison with serum concentrations (~2–3 µg/ml) [17]. Forty-two healthy patients received five doses of 1000 mg once-daily of clarithromycin extended-release and bronchoscopy was performed at 3, 9, 12, 24 and 48 h after the last dose. The highest mean epithelial lining fluid concentration was 27.6 mg/l, measured at 12 h. The 9-h evaluation for alveolar macrophages showed a maximal concentration of 1148 mg/l. Similar findings have been reported for the immediate-release formulation by Patel and colleagues [18]. Several observations may help explain the discordance between the reported *in vitro* resistance (30–35%) rates for *S. pneumoniae* and the continued clinical utility of clarithromycin for community RTIs (~92%). Surveillance data may overstate the resistance of *S. pneumoniae* to macrolides due to issues surrounding the use of CO_2 and E-test for *in vitro* testing, which may result in macrolide MIC values that are one- to eight-times higher than with aerobic methods [19]. Furthermore, as mentioned, there are two mechanisms of resistance associated with macrolides and *S. pneumoniae*, ribosomal methylation (*erm*) selects for higher MIC values (32–256 µg/ml), while efflux pump mutant strains (*mef*) are associated with lower MIC values (2–16 µg/ml) and may be susceptible to higher levels of macrolide antibiotics at the site of infection. It is important to note that the predominant mechanism of resistance identified within the USA is the efflux mechanism [20]. Importantly, host immune defenses play an important role in antimicrobial treatment outcomes and these protective effects might partially explain the discordance between reported surveillance resistance rates and clinical outcomes. The macrolides accumulate within phagocytic cells of the immune system and have both antibacterial and immunomodulating effects, including suppression of pro-inflammatory cytokines, interference with oxidant production by neutrophils and acceleration of neutrophil apoptosis [9]. A recent report by Palmer and colleagues highlights the difficulty in extrapolating *in vitro* resistance to *in vivo* outcomes. The retrospective analysis involving five randomized, double-blind trials (AECB and CAP) for clarithromycin extended-release correlated bacterial outcomes for macrolide-susceptible and macrolide-resistant *S. pneumoniae*. Of the 67 isolates, 59 were susceptible (88%) and eight were resistant (12%) to macrolides. Out of the 59 macrolide-susceptible isolates, 51 (86%), and seven out of eight macrolide-resistant isolates (87%), were eradicated by clarithromycin extended-release [20]. The four macrolide-resistant isolates with MIC values of over 1–32 mg/l in comparison with three out of four isolates with MIC values of under 32 mg/l were eradicated following treatment with clarithromycin extended-release therapy. Given the poorly defined and complex interaction between host, pathogen and the macrolide antimicrobial class, we need to continue to define the best pharmacodynamic models that will help us evaluate the appropriate respiratory diseases, pathogens and hosts to maximize clinical outcomes.

Pharmacokinetics & metabolism

Clarithromycin extended-release tablets provide extended absorption of clarithromycin from the gastrointestinal tract after oral administration [7,10]. Clarithromycin extended-release tablets, in comparison with an equal daily dosage of the immediate-release formulation, provide lower and later steady-state peak plasma concentrations but equivalent 24-h AUCs for both clarithromycin and its microbiologically-active metabolite, 14-OH clarithromycin (FIGURE 2). The administration of clarithromycin extended-release tablets under fasting conditions is associated with an approximately 30% reduction in clarithromycin AUC relative to administration with food, hence clarithromycin extended-release tablets should be administered with food.

In 62 healthy human (male and female) subjects aged 18 to 50 years, steady-state peak plasma clarithromycin concentrations of approximately 2–3 µg/ml were achieved about 5–8 h after oral administration of 1000 mg (2 x 500 mg tablets) clarithromycin extended-release once daily. Steady-state peak plasma concentrations of approximately 0.8 µg/ml were obtained 6–9 h after dosing for the active metabolite, 14-OH clarithromycin [7,10]. The three studies conducted to determine the above pharmacokinetic properties were performed in the US according to multiple-dose, open-label, randomized cross-over designs.

The point estimates of relative bioavailability comparing the extended-release to immediate-release formulation of clarithromycin in regards to AUC0-24 were 0.903–0.946. For the metabolite, 14-OH clarithromycin, the point estimates were 0.969–1.041 [7].

The renal clearance for clarithromycin is relatively independent of dose size and approximates the normal glomerular filtration rate [10]. The major metabolite found in urine is 14-OH clarithromycin. The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not significantly differ from those in normal subjects. However, the 14-OH metabolite was found to be lower in hepatically impaired subjects. Clarithromycin is principally excreted via the liver and kidney in a nonlinear, dose-dependent manner. Clarithromycin can be given at a normal dosage to patients with hepatic impairment and normal renal function but in the presence of severe renal impairment, with or without hepatic dysfunction, dosage should be decreased or dosing intervals should be increased [10].

Clinical efficacy

Various clinical studies were conducted to evaluate the efficacy of clarithromycin extended-release in the treatment of upper and lower respiratory tract infections (TABLE 3). The majority were prospective, multicenter, double-blind studies into which eligible patients (based upon explicit entry criteria summarized in the subsections below) were randomized to active treatment. Exclusion criteria common to all the clinical trials included use of systemic antibiotics within 3 weeks prior to study initiation, significant renal or hepatic impairment, use of medications potentially causing drug interactions, pregnant or lactating women and patients with a hypersensitivity to macrolides.

Acute exacerbation of chronic bronchitis

Three trials were conducted to assess the clinical efficacy of clarithromycin extended-release tablets in the treatment of AECB. Two of the three AECB studies required eligible patients to meet the Anthonisen Type I or II criteria, including increased dyspnea, increased sputum volume and increased sputum purulence [21]. Entry criteria typically defined chronic bronchitis by cough and sputum production for over 3 consecutive months and on most days in a consecutive 2-year period and required a recent presumptive clinical diagnosis of an acute bacterial exacerbation (productive cough with a qualified purulent sputum). Clinical cure was defined as the resolution or improvement (returned to baseline condition) of pretreatment signs and symptoms of infection at the test-of-cure visit without the need for further antibacterial therapy. Clinical failure was defined as no improvement in or worsening of pretreatment signs and symptoms of infection that necessitated additional antibacterial therapy at the test-of-cure study visit. The bacteriologic cure was defined as the absence of study entry pathogens from a repeated culture at the test-of-cure visit [22–24].

Men and women aged 40 years or over with a presumptive diagnosis of AECB were eligible for the study. Patients were required to have a medical history of chronic bronchitis and a productive cough with purulent sputum (>25 white blood cells and <10 squamous epithelial cells per field at x 100 magnification). Clinical signs and symptoms included cough, fever, hoarseness and wheezing. Patients were excluded if they presented with other pulmonary diseases (e.g., radiologic evidence of pneumonia) [22–24].

Adler and colleagues compared a 7-day course of clarithromycin extended-release 1000 mg once daily with a 7-day course of clarithromycin immediate-release 500 mg twice daily. At the test-of-cure visit, 83% (83/100) of patients in the extended-release and 82% (67/82) of patients in the immediate-release group achieved clinical cure; 86% (85/99) and 85% (70/82), respectively, demonstrated bacteriologic cure. Overall pathogen eradication rates were 86% (100/116) in the extended-release group and 88% (86/98) in the immediate-release group. No statistically significant between-treatment differences were observed at the test-of-cure visit in the percentage of patients showing resolution or resolution/improvement in their pretreatment signs and symptoms of AECB, with the following exception. A greater percentage of patients in the clarithromycin extended-release group demonstrated resolution of purulent sputum (96% [89/93] vs. 85% [64/75]; p = 0.028).

Anzueto and colleagues compared a 7-day course of clarithromycin extended-release 1000 mg once daily with a 10-day course of amoxicillin/clavulanate 875/125 mg twice daily. At the test-of-cure visit, 85 and 87% of patients in the clarithromycin and amoxicillin/clavulanate groups, respectively, demonstrated clinical cure. Among the clinically and bacteriologically evaluable patients, 92 and 89% in the clarithromycin and amoxicillin/clavulanate treatment groups, respectively, demonstrated bacteriologic cure. Overall pathogen eradication rates were similar between the two treatment groups, 88% of patients taking clarithromycin and 89% of patients taking amoxicillin/clavulanate. Moreover, isolates of *H. influenzae* that were resistant *in vitro* to clarithromycin before treatment were eradicated in the clarithromycin extended-release treatment group resulting in clinical cure.

In a recent study, Notario and colleagues compared a 5-day course of clarithromycin extended-release 500 mg once daily with a 5-day course of clarithromycin immediate-release 250 mg twice daily. Both formulations demonstrated clinical and bacteriologic cure in patients with AECB, most of whom (94%) had a history of COPD. Resolution and/or improvement of the pretreatment signs and symptoms of AECB was documented in over 90% of patients in each treatment group.

CAP

Internationally recognized guidelines published in North America for the treatment of CAP commonly cite the macrolides as an effective form of treatment [25–28]. The North American guidelines are in agreement regarding the treatment of nonICU in patients with a β-lactam plus macrolide combination or monotherapy with a fluoroquinolone with activity against *S. pneumoniae*. The Centers for Disease Control (CDC), Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) guidelines are in agreement in recommending a macrolide or doxycycline as first-line agents in the treatment to out-patients with CAP. However, the IDSA also recommends antipneumococcal fluoroquinolones as an alternative for first-line therapy. Due to the development of antibacterial resistance in *S. pneumoniae* over the last decade, particularly throughout Europe, some differences regarding the positioning of macrolides are noted among international guidelines [29]. According to a recent review conducted by File and Tan, these differences are attributed to variation in healthcare practices and policies as well as in local antibacterial susceptibilities. For example, in the treatment of out-patients with CAP, the North American guidelines recommend macrolides as first-line agents, whereas the European guidelines generally recommend amoxicillin (with the exception of the German Respiratory Society) as a first-line therapy. Currently, macrolide-resistant *S. pneumoniae* (MRSP) associated with the *mef* gene and a lower level of resistance (<16 µg/ml), predominates in North America, whereas the *erm* gene and a higher level of resistance (>32 µg/ml) predominates in Europe [29].

The 2000 IDSA guidelines cite increasing rates of pneumococcal resistance to macrolides as a source of concern over the possible treatment failure of this class of drugs. However, while pneumococcal rates of resistance to the fluoroquinolones in the USA remain low at under 5% and *in vitro* resistance rates are approaching 25 and 35% for the macrolides and β-lactams respectively, the ATS guidelines point out that treatment failure has not been observed at an appreciable rate [30]. Concerns that overuse of fluoroquinolones may result in increasing resistance have led to the feeling that they be reserved for alternative treatment in situations where high level resistance is suspected or complicating factors exist.

Table 1. Comparative *in vitro* activity of erythromycin, azithromycin and clarithromycin [10].

	Erythromycin (mg/ml)		Azithromycin (mg/ml)		Clarithromycin (mg/ml)	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
S. pneumoniae						
- Pen-susceptible	0.06	0.06	0.06	0.125	0.03	0.06
- Pen-intermediate	0.03	0.06	0.06	0.125	0.03	0.03
- Pen-resistant	0.06	>128	0.125	>128	0.03	>128
S. pyogenes	0.03-0.12	0.03-4	0.12-1	0.12-4	0.012-0.03	0.012-2
M. catarrhalis	0.12-0.5	0.25-2	<0.015-0.12	0.03-0.5	0.06-0.25	0.12-1
H. influenzae	1-8	2-32	0.25-4	0.25-4	1-8	2-16
M. pneumoniae	0.004-0.01	0.004-0.02	0.01-0.03	0.01-0.12	0.004-0.5	0.03-0.5
C. pneumoniae	0.25	0.50	0.25	0.50	0.06	0.50
L. pneumophila	0.1-1	0.5-2	0.12-0.5	0.25-2	0.12-0.25	0.25

Various studies have been conducted comparing the efficacy of clarithromycin to fluoroquinolones. The efficacy of clarithromycin extended-release was compared with the fluoroquinolones, levofloxacin and trovafloxacin, in two separate, double-blind, randomized clinical trials. Men and women 18 years of age or older with two or more signs and symptoms suggestive of CAP, a chest radiograph confirming the presence of infiltrate and a purulent sputum sample were eligible for the studies. Entry criteria included presence of a pulmonary infiltrate on a chest radiograph, purulent sputum production qualified by Gram's stain and multiple symptoms consistent with pneumonia (e.g., chest pain, cough, dyspnea, tachypnea, cyanosis, ausculatory findings and evidence of pulmonary consolidation). Excluded from the study were patients who were residents of a chronic care facility or who were hospitalized within 4 weeks prior to enrolment. Patients with confounding pulmonary diseases (e.g., active tuberculosis, empyema and lung abscess), immunodeficiency, or clinically significant renal or hepatic disease were also excluded [31,32].

In both studies, clinical resolution of signs and symptoms of CAP, bacteriologic eradication of pathogens and clearing of radiographic evidence of pneumonia were determined to assess the efficacy of the clarithromycin extended-release treatment regimen. Clinical response was assessed as cure or failure based upon the 1998 FDA draft guidelines for clinical trials of antimicrobial agents used for the treatment of CAP [33].

Gotfried and colleagues compared a 7-day course of clarithromycin extended-release tablets 1000 mg once daily with a 7-day course of oral levofloxacin (Levaquin®, Ortho-McNeil Pharmaceutical, Inc., NJ, USA) 500 mg daily. Among clinically evaluable patients at the test-of-cure visit, clinical cure rates were 88 and 86% and radiographic success rates were 95 and 88% for clarithromycin extended-release and levofloxacin, respectively. Both treatment regimens were effective in resolving and improving clinical signs and symptoms of CAP. Among clinically and bacteriologically evaluable patients, bacteriologic cure rates were 85 and 88% for clarithromycin extended-release and levofloxacin, respectively. The results demonstrated equivalent efficacy of the two treatment regimens [31].

Sokol and colleagues compared a 7-day course of clarithromycin extended-release tablets 1000 mg daily with a 7-day course of trovafloxacin 200 mg once daily. Due to FDA safety concerns regarding trovafloxacin (Trovan™, Anakena ePharmaceuticals, Barcelona, Spain) the study was prematurely terminated resulting in inadequate power to demonstrate equivalence. However, among clinically evaluable patients at the test-of-cure visit, clinical cure rates were 87 and 95% and radiographic success rates were 95 and 95% for clarithromycin extended-release and trovafloxacin, respectively. In clinically and microbiologically evaluable patients, overall bacteriologic eradication rates were 89 and 96% for clarithromycin extended-release and trovafloxacin, respectively, with no significant differences between groups. Both treatment regimens were effective in resolving and improving clinical signs and symptoms of CAP. Among clinically and bacteriologically evaluable patients, bacteriologic cure rates were 89 and 96% for clarithromycin extended-release and trovafloxacin, respectively. The results demonstrated equivalent efficacy of the two treatment regimens [32].

Pharyngitis

A randomized, double-blind, parallel-group, active controlled multicenter study compared the efficacy of clarithromycin extended-release 500 mg q.d. for 5 days with that of penicillin V 500 mg three-times daily for 10 days in patients with positive rapid immunoassay results for *S. pyogenes* antigen at baseline. Entry criteria required patients to have a sore throat and at least one sign or symptom of streptococcal infection. Patients were required to have positive rapid immunoassay results for the *S. pyogenes* antigen. In the per-protocol population at the

test-of-cure visit, the bacteriological and clinical responses were demonstrated to be equivalent. The bacteriological eradication rates were 89 and 90% and the clinical cures rates were 98 and 94% in the clarithromycin extended-release and penicillin V treatment groups, respectively. Resolution or improvement in sore throat and erythematous pharynx and tonsils (with or without exudates) was observed in 90% or more of the patients in each treatment group [3].

AMS

The efficacy of clarithromycin extended-release tablets was compared with clarithromycin immediate-release tablets in a randomized, double-blind, parallel-group, multicenter study. A clinical diagnosis was based upon medical history, physical exam, signs and symptoms (e.g., facial pain, pressure, tightness over maxillary sinuses and purulent nasal discharge for at least 7 days before but not longer than 28 days before the pretreatment visit). The clinical diagnosis of sinusitis was confirmed radiographically (e.g., presence of opacification, an air/fluid level, or mucosal thickening in one or both maxillary sinuses). Patients with signs, symptoms and a radiologically confirmed diagnosis of AMS were treated with once- or twice-daily clarithromycin for 14 days. At the test-of-cure visit, 85% of patients in the clarithromycin extended-release group and 79% in the immediate-release group were deemed clinical cures; 89 and 91% in the extended-release and immediate-release groups, respectively, demonstrated radiographic success [34].

Postmarketing surveillance

Clarithromycin has an established safety profile in the treatment of respiratory tract infections based upon over 10 years of clinical experience with clarithromycin immediate-release tablets. Spontaneous reports of various drug-related adverse events have been reported ranging from mild allergic reactions of urticaria to rare cases of anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis. There have been reports of thrombocytopenia, leukopenia and neutropenia, tooth discoloration – which is usually reversible with professional dental cleaning – and isolated cases of hearing loss, usually in elderly women. Alterations in the sense of smell, usually in conjunction with taste disturbances, have also been reported. Changes in laboratory values of possible clinical significance reported with clarithromycin have included liver function, renal function and hematologic tests [10].

Transient CNS events and hepatic adverse events have been infrequently reported with clarithromycin but usually resolve with discontinuation of the drug [10]. In very rare instances, fatal hepatotoxicity has occurred, which has generally been associated with serious underlying diseases and/or concomitant medications. The macrolides have also been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsade de pointes. As with most antibacterials, clarithromycin can also cause pseudomembranous colitis ranging in severity from mild to life threatening [10].

Safety & tolerability

The safety of the macrolides in general and clarithromycin in particular, has been well documented. Clarithromycin was first marketed in the USA in 1991. The clarithromycin extended-release formulation was approved for use in the USA in 2001.

As described earlier, clarithromycin is synthesized by substituting the C6 hydroxy group of erythromycin with a methoxy group. The modification of erythromycin to create clarithromycin, via methylation of the C6 hydroxy group yields a macrolide with improved gastrointestinal tolerability. Comparative studies have shown that clarithromycin is better tolerated than either erythromycin base or erythromycin stearate. Investigators have postulated that the improved tolerability of clarithromycin is related to decreased formation of degradation products at low pH, especially hemiketal derivatives.

The tolerability of the clarithromycin extended-release formulation was evaluated for each patient enrolled in the Phase III efficacy trials performed in the USA [36]. The studies performed for application to the FDA for clarithromycin extended-release tablets included two Phase III efficacy trials, clarithromycin immediate-release 500 mg twice daily for 14

Table 2. Pharmacokinetic parameters (mean ± SD) of clarithromycin extended-release and immediate-release formulations [30].

Regimen	C_{max} (mg/l)	T_{max} (h)	C_{min} (mg/l)	AUC0-24 (m/h/l)	DFL
Clarithromycin					
A (ER)	2.59 ± 0. 71	7.8 ± 4.0	0.76 ± 0.37	42.1 ± 13.2	1.08 ± 0.28
B (IR)	3.51 ± 0.98	2.1 ± 0.6	0.91 ± 0.39	46.1 ± 13.8	1.38 ± 0.25
14(R)-OH-clarithromycin					
A (ER)	0.79 ± 0.17	8.7 ± 5.2	0.42 ± 0.13	15.1 ± 3.2	0.60 ± 0.23
B (IR)	0.82 ± 0.16	2.4 ± 1.7	0.42 ± 0.10	14.4 ± 2.9	0.67 ± 0.14

AUC0-24: Area under the plasma concentration-time curve over 24 h after dosing; C_{max}: Peak plasma concentration; C_{min}: Trough plasma concentration; DFL: Degree of plasma concentration fluctuation; ER: Extended-release; IR: Immediate-release; T_{max}: Time to C_{max}.
Adapted from Guay *et al.*, *Clin.Therapeutics* (2001).

days versus clarithromycin extended-release 1000 mg (2 x 500 mg tablets) for 14 days for AMS and clarithromycin immediate-release 500 mg twice daily for 7 days versus clarithromycin extended release 1000 mg (2 x 500 mg tablets) once daily for 7 days for AECB. Study reports indicated comparable patient demographic characteristics for both the AECB and AMS studies. A total of 459 subjects were included in the analysis versus 444 subjects in the immediate-release group. Of the 459 patients that received the extended-release formulation during the Phase III trials, 115 (25.1%) reported at least one adverse event that was considered related to treatment, compared with 92 out of 444 patients (20.7%) taking the immediate-release formulation [36]. The most commonly reported adverse events in the trials are similar to prior adverse events reported for clarithromycin, including diarrhea (6% for extended-release versus 5% for immediate-release), abnormal taste (6 and 6%) and nausea (3 and 5%). Of the reported adverse events, less than 2% were reported as severe. One significant finding concerning tolerability data collected from the Phase III trials, concerns the reported severity of GI events, based on reported severity scores. There was a significant difference reported in favor of the extended-release formulation concerning severity of GI events ($p = 0.018$). The tolerability data also indicated that treatment discontinuation due to G_I events ($p = 0.011$) and taste disturbance ($p = 0.004$) was significantly less with the extended-release formulation. Less than 3% of adult patients who received the clarithromycin extended-release formulation discontinued treatment due to drug-related adverse events.

Tolerability data are also available for two recently completed comparative studies evaluating clarithromycin extended-release versus amoxicillin-clavulanate for AECB and versus levofloxacin for CAP. Anzueto and colleagues reported rates of treatment discontinuations for any reason were lower in the clarithromycin extended-release treatment group compared with the amoxicillin-clavulanate group (3 vs. 12%; $p = 0.005$) for patients being treated for AECB [23]. In the comparative trial for CAP, clarithromycin extended-release tablets (1000 mg daily) had overall reported adverse events that were similar to levofloxacin (500 mg daily), with the exception of taste disturbance, which was reported in 13% of the clarithromycin extended-release group versus 1% for the levofloxacin group ($p < 0.001$) [31].

Table 3. Clarithromycin extended-release studies.

Treatment group (n)	Dosing regimen[§] (days)	Clinical cure (%)	Bacteriologic cure (%)	Ref.
Acute exacerbation of chronic bronchitis				
Clarithromycin ER (100)	1000 mg q.d. x 7 days	83	86	[21]
Clarithromycin IR (82)	500 mg b.i.d. x 7 days	82	85	
Clarithromycin ER (137)	1000 mg q.d. x 7 days	85	92	[22]
Amoxicillin/clavulanate (133)	875/125 mg b.i.d. x 10 days	87	89	
Clarithromycin ER (307)	500 mg q.d. x 5 days	97	89	[23]
Clarithromycin IR (307)	250 mg b.i.d. x 5 days	98	89	
Community-acquired pneumonia				
Clarithromycin ER (128)	1000 mg q.d. x 7 days	88	88	[30]
Levofloxacin (124)	500 mg q.d. x 7 days	86	86	
Clarithromycin ER (85)	1000 mg q.d. x 7 days	87	89	[31]
Trovafloxacin (66)	200 mg q.d. x 7 days	95	96	
Pharyngitis/tonsillitis				
Clarithromycin ER (177)	500 mg q.d. x 5 days	98	89	[33]
Penicillin V (154)	500 mg t.i.d. x 10 days	94	90	
Acute maxillary sinusitis				
Clarithromyicn ER (124)	1000 mg q.d. x 14 days	85	§§	[34]
Clarithromycin IR (123)	500 mg b.i.d. x 14 days	79	§§	

[§]q.d.: Once-daily; b.i.d.: Two-times daily, t.i.d.: Three-times daily.
[§§]This study evaluated clinical and radiologic data only.

Clarithromycin undergoes first-pass metabolism involving the cytochrome P450 system. Specifically, the CYP3A isoform subfamily is theorized to be the principal subfamily involved in clarithromycin metabolism and hence CYP3A4 interactions with coadministered drugs have been reported [10]. Macrolides, including clarithromycin extended-release, should not be coadministered with terfenadine, astemizole, cisparide or pimozide due to an increased risk of QT interval prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes. Other clinically relevant interactions have been reported with carbamazepine, digoxin, warfarin, cyclosporin and theophylline [10].

Conclusion & expert opinion

Clarithromycin extended-release tablets were developed in order to improve market acceptance of clarithromycin for the management of out-patient respiratory tract infections, primarily AECB, CAP and AMS. As mentioned within the context of this review, the new formulation of clarithromycin provides an acceptable once-daily formulation that also provides a marginal improvement in its adverse event profile. The new formulation has been shown to be equivalent to the older immediate-release formulation based on area under the concentration curve pharmacokinetics studies (refer to TABLE 2). Recent clinical studies validate the continued efficacy of clarithromycin extended-release for the treatment of AECB, CAP and AMS.

In order for the macrolide class in general and specifically clarithromycin extended-release to remain a viable first-line choice for the treatment of community-acquired respiratory tract infections, the medical community will need to remain diligent in monitoring the changing susceptibility pattern of the common respiratory pathogens, including *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Antimicrobial resistance for all classes of antimicrobials in both the out- and in-patient settings is becoming a very important patient care issue. Stratton and colleagues has reported penicillin-resistance rates of 35% for *H. influenzae* and 90% for *M. catarrhalis* [37]. Penicillin nonsusceptible rates of greater than 40% have been reported in the US for *S. pneumoniae* [38]. Recent reports of increasing utilization of fluoroquinolones for the treatment of out-patient respiratory tract infections and increasing resistance rates for *S. pneumoniae*, *S. aureus* and *Pseudomonas aeuruginosa* have prompted concerns regarding appropriate antimicrobial utilization [30]. Proper antimicrobial use, not only concerning macrolides but also the fluoroquinolones, β-lactams, and tetracyclines, will hopefully prolong the lifespan of these important antimicrobial classes. Out-patients without significant comorbidities and without significant risk for infection with highly resistant pathogens can continue to be treated with macrolide antimicrobials.

Five-year view

One of the areas for potential future clinical applications concerning the macrolide class of antimicrobials relates to their ability to exert anti-inflammatory/immunmodulatory effects in a significant number of chronic inflammatory conditions, including diffuse panbronchiolitis, chronic sinusitis, cystic fibrosis, asthma and coronary artery disease. The anti-inflammatory effects of macrolides were first suggested in the 1970s [39]. Although the anti-inflammatory mechanisms have been obscured by the possibility of a microbiologic etiology of a disease state, it has now been accepted that macrolides have effects beyond bacterial killing. The degree of anti-inflammatory activity differs among macrolides with the 14-member macrolides clarithromycin, roxithromycin and erythromycin having more effects than 15-member macrolides, such as azithromycin [40].

On a cellular/tissue level, macrolides can modify cytokine production and have effects on neutrophil migration and activation. Most of the data revolve around the effects on interleukin (IL)-8 and TNF-α. In regards to pulmonary diseases, macrolides have been shown to have several salutary effects. These include protecting ciliated epithelium against oxidative damage, membrane stabilizing effects, normalization of mucous secretion and/or properties, effects on bacterial biofilm production, reduction of bronchial hyper-responsiveness, decrease in sputum purulence and a reduction in leukocyte count [41].

The molecular target of the anti-inflammatory effects of the macrolide antibiotics appears to be nuclear factor (NF)-κB and AP-1 transcription factors [42,43]. NF-κB and AP-1 have been shown to both regulate IL-8 expression and the subsequent neutrophil recruitment in airway dieases [44]. Clarithromycin has been shown to attenuate NF-κβ activation induced by TNF-α [45]. Miyanohara reported on the ability of clarithromycin to reduce gene expression of interleukin-1β in fibroblasts and epithelial cells from nasal mucosa by NF-κβ inactivation [46]. Diffuse panbronchiolitis (DPB), an inflammatory disease common in Japan and associated with an untreated 5-year mortality rate of 50%, is recognized as one of the original chronic inflammatory disease states successfully treated with macrolides [47]. DPB presents with cough, airflow limitation, sinusitis, dyspnea, diffuse chronic inflammation of the bronchioles and mucopurulent expectoration. A wide variety of pathogens are found in the sputum of DPB patients, including *H. influenzae*, *S. pneumoniae*, *Klebsiella pneumoniae and S. aureus*. Mucoid *P. aeuruginosa* colonization is very common. Several studies have shown the macrolides, including erythromycin, clarithromycin and azithromycin (Zithromax®) to improve 10-year survival from 12.4% in patients colonized with *P. aeruginosa* to over 90% after 2–3 months of macrolide therapy [48].

Clarithromycin therapy has been evaluated for other chronic inflammatory diseases, including chronic bronchitis and bronchiectasis. Long-term administration of clarithromycin has been associated with decreased sputum volume and increased sputum elasticity [49]. The decreased sputum volume expectorated was found in patients with chronic bronchitis, bronchiectasis and diffuse panbronchiolitis. The authors proposed that the effect was related to inhibition of airway secretory cells by clarithromycin. Recent work published by Tagaya and colleagues suggests that the short-term administration (7 days) of 400 mg/day of clarithromycin, in patients with chronic bronchitis or bronchiectasis without apparent

respiratory tract infection reduced chronic airway hypersecretion by inhibiting chloride secretion and decreased sputum hydration [50]. In the clarithromycin group, 38% of patients had over a 30% reduction in sputum production versus 7% in the amoxicillin group and 0% in the cefaclor group. Further mechanistic and clinical trials should help to broaden our understanding of the beneficial role of macrolides for the treatment of chronic bronchitis and bronchiectasis.

The anti-inflammatory activity of clarithromycin has been studied in adults with chronically inflamed sinus mucosa by MacLeod and colleagues [51]. The Phase IV, open-label study in 25 patients with clinically stable chronic sinusitis and persistent maxillary sinus inflammation were treated for 14 days with clarithromycin 500 mg b.i.d. Statistically significant ($p \leq 0.05$) reductions in pre-treatment sinus mucosal inflammation markers, including CD68, EG2, elastase, IL-6, IL-8, tumor necrosis factor (TNF)-α and edema score were observed. The severity of sinus headache and sinus pain also significantly improved. Yamada and colleagues evaluated the use of clarithromycin 400 mg/day for 8 to 12 weeks in 20 adult patients with nasal polyps due to chronic rhinosinusitis. The study evaluated IL-8 levels in nasal lavage and changes in polyp size. Clarithromycin therapy decreased the size of nasal polyps in 8 of 20 cases. A significant correlation between decreased IL-8 levels and polyp reduction was observed. A high level of IL-8 production pre-treatment was related to a good clinical outcome for nasal polyp size reduction [52].

Macrolide antibiotics, including troleandomycin (TAO®), erythromycin and clarithromycin have been studied for the treatment of asthma and have been shown to decrease corticosteroid use in corticosteroid-dependent asthmatics [53]. Miyatake and colleagues demonstrated a decrease in bronchial hyperresponsiveness following 10 weeks of treatment with erythromycin in 23 patients not treated with oral and inhaled steroids [54]. A double-blind, placebo-controlled, crossover trial by Amayasu and colleagues demonstrated similar results for clarithromycin in 17 asthmatic adults treated for 8 weeks. The study also reported a decrease in blood and sputum eosinophils [55]. Long-term treatment for asthma remains controversial due to implications of potential chronic infection due to *M. pneumoniae* and *C. pneumoniae*. A study by Kraft and colleagues reported the improvement of lung function (FEV1) in 55 asthmatic patients treated with clarithromycin 500mg b.i.d. for 6 weeks. Significant changes were also noted for IL-5, IL-12 and TNF-α. Only subjects PCR positive for *M. pneumoniae* or *C. pneumoniae* showed significant lung function improvement and cytokine changes [56]. Placebo-controlled trials will be needed to further elucidate the potential role of macrolide for the treatment of asthma.

The anti-inflammatory/immunomodulatory effects of the 14- and 15-member macrolides, including clarithromycin, potentially offer new and novel ways to improve the clinical outcomes associated with chronic inflammatory diseases, including chronic sinusitis, asthma, chronic bronchitis and cystic fibrosis. Continued mechanistic studies, supported by double-blind, randomized clinical trials are necessary to further elucidate the role of the macrolides for the treatment of chronic inflammatory diseases.

Key issues

- Clarithromycin extended-release 500 mg tablets are formulated using a patented polymer-based matrix that slows the release of clarithromycin and extends absorption from the gastrointestinal tract after oral administration. Relative to an equal total daily dose of immediate-release clarithromycin tablets, clarithromycin extended-release tablets provide lower and later steady-state peak plasma concentrations but equivalent 24-h area under the plasma concentration–time curve and similar steady-state trough plasma levels for both clarithromycin and its microbiologically active metabolite.
- The new formulation of clarithromycin provides an acceptable once-daily formulation that also provides a marginal improvement in its adverse event profile. The new formulation has been shown to be equivalent to the older immediate-release formulation based on area under the concentration curve pharmacokinetics studies.
- A retrospective analysis was recently completed to determine if increasing resistance rates of *Streptococcus pneumoniae* modified the clinical efficacy of clarithromycin in patients being treated for acute exacerbations of chronic bronchitis and community-acquired pneumonia. Based upon the results of the analysis for three separate acute exacerbations of chronic bronchiti trials and one community-acquired pneumonia trial, increasing rates of reported *in vitro* resistance for *S. pneumoniae* did not have a significant effect on the eradication and clinical response to clarithromycin therapy.
- Appropriate utilization of all antimicrobials, including clarithromycin extended-release, will be necessary to preserve the continued efficacy of antimicrobials for the management of respiratory tract infections. Out-patients without significant comorbidities and without significant risk for infection with highly resistant pathogens can continue to be treated with macrolide antimicrobials, including the extended-release clarithromycin formulation, for CAP, acute maxillary sinusitis and AECB.
- Continued mechanistic studies, supported by double-blind, randomized clinical trials are necessary to further elucidate the role of the macrolides for the treatment of chronic inflammatory diseases, such as chronic sinusitis, asthma, chronic bronchitis and cystic fibrosis.

Information resources

- Abbott Laboratories
  www.rxabbott.com/bx/xl/bxx006.htm
- FDA
  www.fda.gov/cder/guidance/2570dft.pdf
- Centers for Disease Control and Prevention
  www.cdc.gov
- Infectious Diseases Society of America
  www.idsa.org

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